UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/852,910	05/11/2001	Annette Gilchrist	2661-101	4758

6449 7590 12/03/2004

ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 12/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/852,910	GILCHRIST ET AL.	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-101* is/are pending in the application.

4a) Of the above claim(s) *2,10-12,20,25-32 and 34-101* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9,13-19,21-24 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

Claims 1-101 are pending in the application.

Claims 1, 3-9, 13-19, 21-24 and 33 are under examination.

Claims 2, 10-12, 20, 25-32, 34-101 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and specie, as stated above.

Oath/Declaration

In view of the new declaration on the record, the objection is withdrawn.

Specification

In view of the amendments to the specification, the objection to the specification no longer applies.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-11, 13-19, 21-24, 28 and 33, as amended, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method utilizing a

biased library derived from the carboxyl terminus of the Gα-coupled receptor as the peptide library and specific peptide library for the candidate compounds does not reasonably provide enablement for a method using any or all types of G-protein coupled receptor (GPCR) for the peptide library or candidate compounds for reasons advanced in the last Office action, 4/17/03.

Response to Arguments

Applicants argue that the method of claim 1 is a screening assay method that allows one to identify desired compounds. It is argued that not all compounds subject to a screen will provide a positive result.

In response, if a compound has no definite or given structure in the cchemical library, then it is not seen how screening can be done. While not all compounds will obviously provide a positive result however, there must be a reasonable assurance that the compounds applicants desire is obtained. That is, high affinity compounds relative to the native one.

Applicants argue that the invention does not relate to methods using an infinite combination of any G protein coupled receptor with any library, but a finite combination of a G protein coupled receptor with a library based on sequences from a cognate G protein. The method can and does work with any G

protein coupled receptor since the library used in each case is based on the sequence of the partner protein for the G protein coupled receptor, namely the G protein.

In reply, just how exactly a compound in a library can be based on a cognate G protein is positively not recited in the claims. Is this based on the primary sequence or tertiary sequence of the G cognate protein? If on the primary sequence, is there just one binding site of the G cognate protein? Is this based on deleting, substituting or adding, singly or in combinations, the different residues of a cognate G protein? What is the length of the cognate sequence that results in a library or the size of the library that produces a compound? Thus, even for this single parameter of a library based on a cognate G protein, already too numerous, unpredictable factors come into play. This is not to mention the various combinations of this parameter with the also undefined structures of the other claimed variables e.g., inhibitory substance. The evidence provided in the specification relates to a single based library of definite structure for different G protein coupled receptors.

Applicants argue that since G proteins have been cloned and sequenced, and since the prior art already has identified Gα and Gβγ regions that are implicated in G protein coupled receptor binding, it involves no experimentation to develop a library

from any of these sequences according to the methods described in detail in the specification.

In response, the cloning and sequencing of some, not all, of G proteins do not indicate whether in fact binding is mainly in the Gα and Gβγ regions. One of the argued references, Azpiazu states that G protein βγ complex has been shown to directly modulate effector function and is required for receptor interaction of the G protein, the individual functions of these γ are still unclear. (See page 35305 col. 1.) Furthermore, at page 35308 Azpiazu states that the results of the studies indicate that there may be selectivity in the interaction between γ subunits types and receptors. See also page 35307 that states that inhibition by of e.g., somatostatin was not affected by the γ5 peptide. The other reference, Blahos are still in the stage of identifying peptides that would bind G protein receptors. Contrary to applicants' assertion none of these references made a library. Rather, individual components were tested to determine its inhibitory effect for a specific type of G protein receptor.

Applicants argue that any skilled molecular biologist could, using the common knowledge in the field concerning G protein binding and sequence, can make a library based on any G protein sequence known or later shown to bind a G protein

coupled receptor. If an appellants choose to rely upon general knowledge in the art to render his disclosure enabling, the applicants must show that anyone skilled in the art would have actually possessed the knowledge, In re Lange (CCPA 1981) 644 F2d 856, 209 USPQ 288, or would reasonably be expected to check the source which applicants rely upon to complete his disclosure and would be able to locate the information with no more than reasonable intelligence. There is no explicit description in the specification as to the method of screening any library of such huge scope as recited in the generic claim. Applicants can rely upon prior art, which would enable one skilled in the art to glean therefrom the necessary information to render the specification enabling. But the burden is on applicant to point out precisely where enablement lies in such disclosure. In re Albrecht II (CCPA 1975) 185 USPQ 590. However, not everything which may be cited as prior art to preclude the grant of a patent can be equated with common knowledge for the purposes of meeting the enablement requirement of 112.

Applicants argue that once a G protein coupled receptor is chosen, it is a simple matter to either select from among the G proteins known to bind to perform binding assays to select a previously unknown binder from among other G proteins.

In response, as stated in the disclosure at page 1, G protein coupled receptors include a wide range of receptors such as hormone, viral, growth factor, chemokine and so forth. As shown by the newly submitted references, the unpredictability of such reactions of a ligand to known receptors cannot even be predicted a priori except through experimental studies.

Applicants argue that the specification, Tables II and III, provides dozens of exemplary sequences obtained using several different libraries each containing millions of peptide members.

In response, [0054] alludes to this different peptides but states that only random substitutions of these amino acids are made into a library i.e., a specific type of modifications within a specific type of peptide of defined length.

Applicants argue that the method is not performed in vivo.

In reply, the claims recite for intracellular location or binding of the peptide members to a G protein receptor, which appears to read on in vivo testing.

Applicants argue that the claimed invention does not claim a peptide library per se or a vector or expression system. Such libraries and vectors are known.

In reply, while the invention is not directed per se to the library, vector or expression system however, these components are necessary to execute the methods. It is not seen how the method can be manipulated or operated without any of these components.

Applicants argue that Tables IX and X of the specification show two different composition of rhodopsin with based library. Tables XI, XII and XIII for PARI with a Gq based library and the other tables for other receptors based on other library.

In response, this specific showing is not controverted. What is controverted is the huge scope of the claims without reciting a particular kind of library or a receptor or other specific embodiments as enabled in the specification. Applicants cannot read limitations in the specification into the claims. Protein-protein interactions and inhibition of such reactions has never been known to be a mere routine endeavor, as evident from the different newly submitted references. As evident from the experiments in the specification, this specific peptide library as used in the method, which binds to a specific receptors, unexpectedly fail to produce the expected results for some of the peptides in the library. Also, see the disclosure at page 16, paragraph [0046] that discloses that the interaction

between a G protein and a GPCR is quite specific. For example, a difference in one amino acid can substantially reduce or eliminate the ability of a G protein peptide to bind to its receptor. In support of this, see Osawa et al (The Journal of Biological Chemistry) at page 31052, the abstract.

Claim Rejections - 35 USC § 112

In view of the amendments to the claims and applicants' arguments, the rejections of the claims under this statue have been obviated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3-11, 13-19, 21-24 and 33 are rejected under 35 U.S.C. 103(a) as being obvious over Coughlin et al (U.S. 5,892,014) or Fowlkes et al (WO 98/19162) in view of Gilchrist (The Journal of Biological Chemistry) for reasons set forth in the Office action of 4/17/03.

Response to Arguments

Applicants argue that Coughlin is limited to methods involving extracellular ligands and does not involve G protein/G protein coupled receptor interactions. Applicants acknowledge that Gilchirst discloses certain Gα peptide analogs that can disturb the molecular interface occurring between a G protein and a G protein coupled receptor. But argue that there is no disclosure in Gilchirt of a methodology on how to use these Gα peptide analogs to identify specific inhibitors of G protein coupled receptors.

In reply applicants' attention is directed to Gilchrist's disclosure specifically at page 14917, DISCUSSION heading that states that "…by using a random peptides on plasmid library approach……..we identified several analogs of the native Gαt (340-350) that bind with high affinity to rhodopsin…. As the Gαi2 and Gα i3 diverge by just one and two amino acids from Gαt carboxyl-terminal sequence,… we evaluated the effects of the native Gα and analog peptides on receptor coupling to Gi proteins…… Gα..(344-354)…inhibited specific binding… the result suggests that synthetic peptides corresponding to Gα i1/2…carboxyl-terminal sequences interrupt the interaction between A1 adenosine receptors and Gi proteins…." (Underlinings

supplied.) Thus, Gilchrist, even alone, discloses finding (identifying as claimed) the inhibitors for G protein coupled receptors and its ligand, G protein. The fact that some of the peptide in the library acts as agonist and some as antagonist does not detract from the findings that Gilchrist screened the library for its inhibitory (antagonist) effect.

Applicants argue that Fowlkes at page 128 relates to purified estrogen receptor, nuclear hormone receptor and not a G protein coupled receptor.

In reply, Fowlkes does not limit the teachings to only estrogen receptors but recites other receptors. The other receptors are disclosed at page 24, lines 15-30 which recites the different species of G-protien receptors. [Hormone receptor is a species or included in the G-protein coupled receptors as discussed by applicants in the Background art at page 1 of the instant disclosure.] Applicants argue that Fowlkes discloses that complementary library is often less specific in their binding to the target protein than are the members of the first library indicates to the skilled person that the methods are not designed to and cannot achieve the methods claimed here and destroy any possible motivation to combine them.

In response, the findings of Fowlkes that some of the complementary library, not all, are less specific does not

detract from the finding of obviousness. In the absence of any evidence that the complementary library of Fowlkes is less specific, applicants' arguments are merely conclusory. Obviousness does not require absolute predictability. Thus, Fowlkes, even alone and Gilchrist, also by itself, renders the claimed method prima facie obvious.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This application contains claims 2, 12, 20, 25-32and 34-101 drawn to nonelected invention. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
November 22, 2004